**Drug treatment**

**Expert Opin Investig Drugs. 2017 Aug 17. [Epub ahead of print]**

**Current Drug and Molecular Therapies for the Treatment of Atrophic Age-Related Macular Degeneration: Phase I to Phase III Clinical Development.**

Li H, Chintalapudi SR, Jablonski MM.

**INTRODUCTION:** Age-related macular degeneration (AMD) is the leading cause of vision loss among the elderly. Atrophic AMD, including early, intermediate and geographic atrophy (GA), accounts for ~90% of all cases. It is a multifactorial degeneration characterized by chronic inflammation, oxidative stress and aging components. Although no FDA-approved treatment yet exists for the late stage of atrophic AMD, multiple pathological mechanisms are partially known and several promising therapies are in various stages of development. Areas covered: Underlying mechanisms that define atrophic AMD will help provide novel therapeutic targets that will address this largely unmet clinical need. The purpose of this paper is to review current promising drugs that are being evaluated in clinical trials. Because no pharmacological treatments are currently available for late stage of atrophic AMD, any new therapy would have extensive market potential.

**Expert Opinion:** The number of AMD patients is predicted to increase to ~30 million worldwide by 2020. In response to this enormous unmet clinical need, new promising therapies are being developed and evaluated in clinical trials. We propose that the assessment of novel interventions will also need to consider the genotypes of participants, as the benefit may be determined by polymorphisms in an individual's genetic background.

**PMID:** 28816076

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**BMC Ophthalom. 2017 Aug 18;17(1):147.**

**Predictive models of long-term anatomic outcome in age-related macular degeneration treated with as-needed Ranibizumab.**

Gonzalez-Buendia L, Delgado-Tirado S, Sanabria MR, Fernandez I, Coco RM.

**BACKGROUND:** To analyze predictors and develop predictive models of anatomic outcome in neovascular age-related macular degeneration (AMD) treated with as-needed ranibizumab after 4 years of follow-up.

**METHODS:** A multicenter consecutive case series non-interventional study was performed. Clinical, funduscopic and OCT characteristics of 194 treatment-naïve patients with AMD treated with as-needed ranibizumab for at least 2 years and up to 4 years were analyzed at baseline, 3 months and each year until the end of the follow-up. Baseline demographic and angiographic characteristics were also evaluated. R Statistical Software was used for statistical analysis. Main outcome measure was final anatomic status.
RESULTS: Factors associated with less probability of preserved macula were diagnosis in 2009, older age, worse vision, presence of atrophy/fibrosis, pigment epithelium detachment, and geographic atrophy/fibrotic scar/neovascular AMD in the fellow eye. Factors associated with higher probability of GA were presence of atrophy and greater number of injections, whereas male sex, worse vision, lesser change in central macular thickness and presence of fibrosis were associated with less probability of GA as final macular status. Predictive model of preserved macula vs. GA/fibrotic scar showed sensibility of 77.78% and specificity of 69.09%. Predictive model of GA vs. fibrotic scar showed sensibility of 68.89% and specificity of 72.22%.

CONCLUSIONS: We identified predictors of final macular status, and developed two predictive models. Predictive models that we propose are based on easily harvested variables, and, if validated, could be a useful tool for individual patient management and clinical research studies.

PMID: 28821236 PMCID: PMC5563005

Retina. 2017 Aug 16. [Epub ahead of print]

ULTRASONOGRAPHIC FINDINGS IN THE VITREOUS OF PATIENTS WITH AGE-RELATED MACULAR DEGENERATION TREATED WITH INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR INJECTIONS.


PURPOSE: We aimed to assess the relationship of repeated intravitreal injection of anti-vascular endothelial growth factor, the main treatment for exudative age-related macular degeneration, with changes in vitreous ultrasonographic findings in patients with age-related macular degeneration.

METHODS: We retrospectively collected data from 41 patients (41 age-related macular degeneration eyes, 41 control eyes) on age, sex, number of injections, and type of anti-vascular endothelial growth factor (ranibizumab, aflibercept). Ocular ultrasonography was performed with open eyelids, under topical anesthesia, and using carbomers as ultrasonographic gel. Topographic, quantitative, and kinetic ultrasonography was performed in all eye quadrants using a 10-MHz posterior pole probe, and vitreous reflectivity was assessed.

RESULTS: The mean age of patients was 79 (range: 59-94) years, with a mean of five intravitreal anti-vascular endothelial growth factor injections (range: 1-13). No significant ultrasonographic differences were found relative to the incidence of partial or complete posterior vitreous detachment. Vitreous hyperechogenicity increased in the treated eye (P < 0.001), and the vitreous reflectivity range increased with the number of injections (P = 0.041, R = 0.214). However, the type of anti-vascular endothelial growth factor used and the time elapsed since the last intravitreal injection was not significant (P > 0.05).

CONCLUSION: These preliminary results indicate a proportional increase in ultrasonographic reflectivity of vitreous gel with the number of injections.

PMID: 28820850

Retina. 2017 Aug 16. [Epub ahead of print]

RANIBIZUMAB AND AFLIBERCEPT FOR THE TREATMENT OF PIGMENT EPITHELIAL DETACHMENT IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: Data from an Observational Study.

PURPOSE: To assess the effect of intravitreal ranibizumab and aflibercept on retinal pigment epithelial detachment (RPED) in patients with neovascular age-related macular degeneration.

METHODS: This was a retrospective analysis of data from a prospectively designed and implemented clinical audit. Analysis included change in RPED dimensions and visual acuity in 92/233 treatment-naive eyes with neovascular age-related macular degeneration and RPED 6 months after treatment with either aflibercept or ranibizumab.

RESULTS: There was no significant between-group difference in the adjusted mean change for maximum RPED height (P = 0.195), diameter (P = 0.522) or visual acuity (P = 0.836) at 6 months. Injection frequency was the only clinical variable that affected RPED height (P = 0.050) and visual acuity change for both treatment groups (P = 0.004). Around 30% of eyes in each group had complete resolution of RPED at 6 months.

CONCLUSION: Eyes with neovascular age-related macular degeneration and RPED showed significant functional and anatomical responses after 6 months of intravitreal anti-vascular endothelial growth factor injections. However, we found no significant difference in anatomical response or change in visual acuity between eyes treated with ranibizumab compared with aflibercept. Larger, prospectively designed, randomized studies with longer term follow-up may identify a difference between the two drugs that we did not detect.

PMID: 28820848

J Fr Ophtalmol. 2017 Aug 10. [Epub ahead of print]

[Inefficacy of aflibercept in the treatment of idiopathic macular telangiectasia type 2 without neovascularization]. [Article in French]

Bénichou J, Soler V, Denis D, Matonti F.

Abstract: Idiopathic macular telangiectasia type 2 is a rare disease consisting primarily of bilateral macular capillary telangiectasia, alterations of the ellipsoid zone and intraretinal cysts that may appear as cystoid macular edema in the absence of neovascularization. Our goal was to study the efficacy of aflibercept in the treatment of these cysts. Thus, we performed a series of three intravitreal injections of aflibercept in the right eye of a woman with a typical presentation of macular telangectasia type 2 complicated by cystoid macular edema without neovascularization. These injections did not significantly improve the anatomical or functional results. Other studies investigating the efficacy of other anti-VEGF in this disease led mainly to a decrease in macular thickness on OCT after injection, without any functional improvement. The anti-VEGFs therefore appear to be of little value in treating MacTel 2 intraretinal cysts without neovascularization.

PMID: 28803666


Long-term outcomes with as-needed aflibercept in diabetic macular oedema: 2-year outcomes of the ENDURANCE extension study.


BACKGROUND/AIMS: To evaluate the efficacy and safety of individualised 2.0 mg intravitreal aflibercept retreatment for diabetic macular oedema (DME) through the fifth year of management.

METHODS: This is a phase IV, 2-year, open-label extension study. Sixty patients completing the 3-year VISTA DME (Study of Intravitreal Aflibercept Injection in Patients With Diabetic Macular Edema) phase III trial enrolled in the ENDURANCE (Long-Term Efficacy and Safety of Intravitreal Aflibercept for the
Treatment of DME in Subjects Who Completed the VISTA DME Trial) extension study. All patients received aflibercept in the presence of clinically relevant DME. Intervals between visits were prescribed according to disease activity. The main outcome measure was mean aflibercept injections given through 2 years.

RESULTS: A mean of 7.7 aflibercept injections were administered through 2 years. Fifteen (25%) patients required no retreatment and 48% (n=29) of patients received five or fewer injections through 2 years. Among patients who received at least one aflibercept retreatment during ENDURANCE, the mean number of injections through 2 years was 9.5. The mean visual acuity and central retinal thickness gains achieved during VISTA DME were maintained and stable during ENDURANCE. The most notable safety signal was progression of diabetic retinopathy. Six (10%) patients converted from non-proliferative to proliferative diabetic retinopathy (PDR), and a total of eight patients experienced PDR events occurring at a mean of 387 days following the previous aflibercept treatment.

CONCLUSION: The need for aflibercept retreatment was substantially reduced in the fourth and fifth years of aflibercept dosing for DME following initiation of therapy in the VISTA DME trial. While vision gains achieved during the 3-year VISTA DME trial were maintained through ENDURANCE with a reduced treatment burden, clinically relevant worsening of diabetic retinopathy was observed with progression to PDR in 10% of the eyes.

PMID: 28814412


Systemic Associations with Residual Subretinal Fluid after Ranibizumab in Diabetic Macular Edema.

Tsai MJ, Hsieh YT, Shen EP, Peng YJ.

PURPOSE: To investigate the impact of systemic diseases on the occurrence of subretinal fluid (SRF) in diabetic macular edema (DME) and prognostic factors for residual SRF following three consecutive monthly intravitreal ranibizumab.

METHODS: Ninety-seven eyes from 68 patients with DME who completed 3 consecutive monthly injections of ranibizumab were enrolled. Systemic parameters mainly included chronic kidney disease (CKD), hypertension, HbA1c, and insulin dependence. Renal parameters for CKD were serum creatinine, estimated glomerular filtration rate (eGFR), and serum albumin. Ocular factors were baseline central macular thickness (CMT), severity of diabetic retinopathy (DR), and status of panretinal photocoagulation (PRP).

RESULTS: Chronic kidney disease had significant correlation with baseline SRF (R = 0.397, p < 0.001 after partial correlation with adjustment for age and DR severity). As for CKD, lower serum albumin, but not eGFR or serum creatinine, was associated with baseline presence of SRF (p = 0.026, p = 0.08 and p = 0.53, resp., after adjustment for age and DR severity). Overall, lower eGFR and lower HbA1c values, contrary to popular belief, predicted the presence of residual SRF following intravitreal injections (p = 0.016 and p < 0.001, resp.).

CONCLUSIONS: Tight sugar control and poorer baseline kidney function may slow the resorption of SRF after anti-VEGF injections in patients with DME in the short term.

PMID: 28819567 PMCID: PMC5551529


Nicolò M, Bonetto M, Rosa R, Musetti D, Musolino M, Traverso CE, Giacomini M.

AIM: Real-life evaluation in the management of patients affected by macular edema secondary to retinal vein occlusion.

MATERIAL AND METHODS: A retrospective, observational study using the I-Macula Web platform.

RESULTS: Thirty-five patients (37 eyes; 15 females and 20 male) affected by RVO were analysed. At 12 months, there was a statistically significant improvement of best-corrected visual acuity (p = 0.0235) and central macular thickness (p < 0.0001). The mean change in visual acuity was 8.9 letters. Twenty-seven eyes underwent DEX implant (n = 62; mean: 2.29) only. Of these, 8, 4, 14, and 1 eyes underwent 1, 2, 3, and 4 DEX implants, respectively. The remaining 10 eyes were also injected with ranibizumab (n = 49; mean: 4.9). At 12 months, 12 eyes (32.5%) presented a dry macula, whereas the remaining 25 eyes (67.5%) still had macular edema. Mean interval between the first and second treatment (T1) and between the second and third treatment (T2) were 5.15 and (T2) 3.7 months, respectively. Where only DEX implants were received, T1 and T2 was 5.1 and 4.9 months, respectively.

CONCLUSIONS: This study confirms that DEX implants and/or anti-VEGF drugs improve visual acuity and central macular thickness in patients affected by RVO.

PMID: 28811936 PMCID: PMC5546074


Sustained Benefits of Ranibizumab with or without Laser in Branch Retinal Vein Occlusion: 24-Month Results of the BRIGHTER Study.


PURPOSE: To evaluate the long-term (24-month) efficacy and safety of ranibizumab 0.5 mg administered pro re nata (PRN) with or without laser using an individualized visual acuity (VA) stabilization criteria in patients with visual impairment due to macular edema secondary to branch retinal vein occlusion (BRVO).

DESIGN: Phase IIIb, open-label, randomized, active-controlled, 3-arm, multicenter study.

PARTICIPANTS: A total of 455 patients.

METHODS: Patients were randomized (2:2:1) to ranibizumab 0.5 mg (n = 183), ranibizumab 0.5 mg with laser (n = 180), or laser (with optional ranibizumab 0.5 mg after month 6; n = 92). After initial 3 monthly injections, patients in the ranibizumab with or without laser arms received VA stabilization criteria-driven PRN treatment. Patients assigned to the laser arm received laser at the investigator’s discretion.

MAIN OUTCOME MEASURES: Mean (and mean average) change in best-corrected visual acuity (BCVA) and central subfield thickness (CSFT) from baseline to month 24, and safety over 24 months.

RESULTS: A total of 380 patients (83.5%) completed the study. Ranibizumab with or without laser led to superior BCVA outcomes versus laser (monotherapy and combined with ranibizumab from month 6; 17.3/15.5 vs. 11.6 letters; P < 0.0001). Ranibizumab with laser was noninferior to ranibizumab monotherapy (mean average BCVA change: 15.4 vs. 15.0 letters; P < 0.0001). However, addition of laser did not reduce the number of ranibizumab injections (mean injections: 11.4 vs. 11.3; P = 0.4259). A greater reduction in CSFT was seen with ranibizumab with or without laser versus laser monotherapy over 24 months from baseline (ranibizumab monotherapy -224.7 μm, ranibizumab with laser -248.9 μm, laser [monotherapy and combined with ranibizumab from month 6] -197.5 μm). Presence of macular ischemia did not affect BCVA outcome or treatment frequency. There were no reports of neovascular glaucoma or iris neovascularization. No new safety signals were identified.
CONCLUSIONS: The BRIGHTER study results confirmed the long-term efficacy and safety profile of PRN dosing driven by individualized VA stabilization criteria using ranibizumab 0.5 mg in patients with BRVO. Addition of laser did not lead to better functional outcomes or lower treatment need. The safety results were consistent with the well-established safety profile of ranibizumab.

PMID: 28807635


Treat-and-Extend Therapy Using Afilbercept for Neovascular Age-Related Macular Degeneration: A Prospective Clinical Trial.

DeCroos FC, Reed D, Adam MK, Salz D, Gupta OP, Ho AC, Regillo CD.

Author information

PMID: 28803629

Other treatment & diagnosis


Inner nuclear layer cystoid spaces are a poor prognostic factor in typical age-related macular degeneration and polypoidal choroidal vasculopathy.

Kang EC, Choi S, Koh HJ.

PURPOSE: To investigate predictive factors for changes in best-corrected visual acuity (BCVA) at 24 months after intravitreal ranibizumab (IVR) for neovascular age-related macular degeneration (nAMD).

METHODS: This retrospective study included 55 eyes of 55 consecutive patients (32 men and 23 women) with nAMD who received three consecutive monthly IVR injections and were re-treated as needed over a 24-month period. We used the mean changes in logarithm of the minimal angle of resolution (logMAR) BCVA at 24 months as the dependent variable in regression analysis.

RESULTS: The presence of intraretinal cystoid spaces in the inner nuclear layer (INLc, P = 0.004) and baseline subfoveal choroidal thickness (SFCT, P = 0.013) predicted BCVA changes from baseline to 24 months. The presence of INLc and thinning of SFCT were associated with decreased BCVA at 24 months. Thirty-five eyes without INLc showed improved logMAR BCVA, from 0.550 ± 0.273 to 0.368 ± 0.274 (P = 0.045); however, 20 eyes with INLc showed decreased logMAR BCVA, from 0.708 ± 0.347 to 0.971 ± 0.523 (P < 0.001) through the 24-month follow-up. The mean number of IVR injections during the follow-up period was 8.74 ± 4.76 in eyes without INLc and 10.63 ± 4.72 in eyes with INLc, without a statistically significant difference (P = 0.144).

CONCLUSION: Eyes with INLc or thinned SFCT showed worse visual outcomes compared with eyes without the INLc or with thick SFCT. Furthermore, eyes without INLc showed improved BCVA; however, eyes with INLc showed decreased BCVA with an as-needed regimen.

PMID: 28819823


EN FACE VERSUS 12-LINE RADIAL OPTICAL COHERENCE TOMOGRAPHY SCAN PATTERNS FOR DETECTION OF MACULAR FLUID IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.
Adam MK, Shahlaee A, Samara WA, Maguire JI, Ho AC, Hsu J.

PURPOSE: To compare fluid detection of autosegmented en face to 12-line radial spectral domain optical coherence tomography scan patterns in neovascular age-related macular degeneration.

METHODS: Retrospective observational case series. Sixty-seven patients (94 eyes) with neovascular age-related macular degeneration underwent autosegmented en face optical coherence tomography (with associated 304-line raster scan) and 12-line radial scan patterns. Sensitivity and specificity of fluid detection for en face scan and 12-line radial scans were determined by combining radial and 304-line raster scans as a gold standard.

RESULTS: Two hundred and fifty-eight en face and 12-line radial spectral domain optical coherence tomography scans were interpreted. Seventy-five scans (58.1%) had fluid, whereas 54 scans (41.9%) did not. En face scan pattern fluid detection sensitivity and specificity was 89.3% and 61.1%, respectively. Twelve-line radial scan pattern fluid detection sensitivity and specificity was 97.3% and 100%, respectively. The difference in fluid detection between scan patterns was statistically significant (P = 0.01). Decreased central macular thickness was associated with false-positive (P = 0.035) and false-negative (P = 0.01) fluid detection on en face scans.

CONCLUSION: En face optical coherence tomography alone is not as sensitive or specific as the 12-line radial scan pattern in detecting fluid in neovascular age-related macular degeneration. En face scans should be corroborated with other optical coherence tomography protocols to guide clinical decision making.

PMID: 28816861

J Histochem Cytochem. 2017 Aug 1;22155417726507. [Epub ahead of print]

Age-Related Changes in the Chorioretinal Junction: An Immunohistochemical Study.

Gupta T, Saini N, Arora J, Sahni D.

Abstract: The chorioretinal junction comprises the retinal pigment epithelium, Bruch's membrane (BM), and adjacent choroidal capillaries. Its significance lies in its ability to support the retina mechanically and metabolically. The aim of this cross-sectional study was to record the senescent changes affecting all the constituents of the chorioretinal junction in 40 histological specimens across the whole spectrum of the adult age range. This study included light microscopy, with hematoxylin and eosin and PAS stains, and fluorescent microscopy. Immunohistochemistry was done using antibodies against neurofilament, synaptophysin, S-100, and collagen IV. The descriptive microanatomy was corroborated by morphometry. The amount of melanin and lipofuscin granule and drusens were noted. The ratio of thickness of BM to capillary diameter reduced from 1:6 or less in the 2nd decade to 1:3 in the 10th decade. Complete hyalinization of intercapillary pillars was seen in the 10th decade. The accumulation of lipofuscin with age was documented with the diminution in the size of epithelial cells. The subepithelial accumulation of drusen was first noted in the specimen from the late 60s. We have described all senescent changes in the chorioretinal junction chronologically. Similar changes are found in a more pronounced form in age-related macular degeneration. These data might serve as a reference baseline for clinicians and pathologists.

PMID: 28813619


Spatial Correspondence Between Intraretinal Fluid, Subretinal Fluid, and Pigment Epithelial Detachment in Neovascular Age-Related Macular Degeneration.

Klimscha S, Waldstein SM, Schlegl T, Bogunovic H, Sadeghipour A, Philip AM, Podkowinski D, Pablik E,
Zhang L, Abramoff MD, Sonka M, Gerendas BS, Schmidt-Erfurth U.

PURPOSE: To identify the spatial distribution of exudative features of choroidal neovascularization in neovascular age-related macular degeneration (nAMD) based on the localization of intraretinal cystoid fluid (IRC), subretinal fluid (SRF), and pigment-epithelial detachment (PED).

METHODS: This retrospective cross-sectional study included spectral-domain optical coherence tomography volume scans (6 x 6 mm) of 1341 patients with treatment-naïve nAMD. IRC, SRF, and PED were detected on a per-voxel basis using fully automated segmentation algorithms. Two subsets of 37 volumes each were manually segmented to validate the automated results. The spatial correspondence of components was quantified by computing proportions of IRC-, SRF-, or PED-presenting A-scans simultaneously affected by the respective other pathomorphologic components on a per-patient basis. The median across the population is reported. Odds ratios between pairs of lesions were calculated and tested for significance pixel wise.

RESULTS: Automated image segmentation was successful in 1182 optical coherence tomography volumes, yielding more than 61 million A-scans for analysis. Overall, 81% of eyes showed IRC, 95% showed SRF, and 92% showed PED. IRC-presenting A-scans also showed SRF in a median 2.5%, PED in 32.9%. Of the SRF-presenting A-scans, 0.3% demonstrated IRC, 1.4% PED. Of the PED-presenting A-scans, 5.2% contained IRC, 2.0% SRF. Similar patterns were observed in the manually segmented subsets and via pixel-wise odds ratio analysis.

CONCLUSIONS: Automated analyses of large-scale datasets in a cross-sectional study of 1182 patients with active treatment-naïve nAMD demonstrated low spatial correlation of SRF with IRC and PED in contrast to increased colocalization of IRC and PED. These morphological associations may contribute to our understanding of functional deficits in nAMD.

PMID: 28813577

Pathogenesis

J Comp Neurol. 2017 Aug 17. [Epub ahead of print]

Juxtanodin in Retinal Pigment Epithelial Cells: Expression and Biological Activities in Regulating Cell Morphology and Actin Cytoskeleton Organization.

Liang F, Hwang JH, Tang NW, Hunziker W.

Abstract: Juxtanodin (also known as ermin) was initially identified as an actin cytoskeleton-related oligodendroglial protein in the rat central nervous system. It was subsequently also found in the rat olfactory neuroepithelium, especially at the apical junctional belt of the sustentacular cells. We further examined juxtanodin expression and functional roles in the retina using fluorescence histochemistry, confocal microscopy, immuno-electron microscopy, molecular biology and cell culture. Prominent juxtanodin expression was found in the photoreceptor-supporting retinal pigment epithelium (RPE), especially in a zone corresponding to the apices of RPE cells, at the roots of the RPE microvilli, and at the base of RPE cells next to the Bruch's membrane. Partial co-localization of juxtanodin immunoreactivity with F-actin (labeled with phalloidin) was observed at the apices and bases of RPE cells. No juxtanodin was detected in other cell types of the retina. In cultured human RPE cell line ARPE-19, expression of extrinsic juxtanodin up-regulated formation of actin cytoskeleton stress fibers, caused redistribution of more F-actin fibers to the cell periphery, and promoted spreading/enlargement of transfected cells. These findings suggest possible roles of juxtanodin in RPE molecular transport, phagocytosis and formation of outer blood-retinal barrier, or possible involvement of juxtanodin expression perturbations in pathogenesis of such retinal disorders as proliferative vitreoretinopathy and age-related macular degeneration. This article is protected by copyright. All rights reserved.

PMID: 28815590


Minasyan L, Sreekumar PG, Hinton DR, Kannan R.

Abstract: Age-related macular degeneration (AMD) is the leading cause of severe and irreversible vision loss and is characterized by progressive degeneration of the retina resulting in loss of central vision. The retinal pigment epithelium (RPE) is a critical site of pathology of AMD. Mitochondria and the endoplasmic reticulum which lie in close anatomic proximity to each other are targets of oxidative stress and endoplasmic reticulum (ER) stress, respectively, and contribute to the progression of AMD. The two organelles exhibit close interactive function via various signaling mechanisms. Evidence for ER-mitochondrial crosstalk in RPE under ER stress and signaling pathways of apoptotic cell death is presented. The role of humanin (HN), a prominent member of a newly discovered family of mitochondrial-derived peptides (MDPs) expressed from an open reading frame of mitochondrial 16S rRNA, in modulation of ER and oxidative stress in RPE is discussed. HN protected RPE cells from oxidative and ER stress-induced cell death by upregulation of mitochondrial GSH, inhibition of ROS generation, and caspase 3 and 4 activation. The underlying mechanisms of ER-mitochondrial crosstalk and modulation by exogenous HN are discussed. The therapeutic use of HN and related MDPs could potentially prove to be a valuable approach for treatment of AMD.

PMID: 28814984 PMCID: PMC5549471


Monocyte infiltration and proliferation reestablish myeloid cell homeostasis in the mouse retina following retinal pigment epithelial cell injury.

Ma W, Zhang Y, Gao C, Fariss RN, Tam J, Wong WT.

Abstract: Age-related macular degeneration (AMD), a leading contributor of vision loss, currently lacks comprehensive treatment. While AMD histopathology involves retinal pigment epithelium (RPE) injury associated with immune cell infiltration, the nature of immune cell responses to RPE injury remains undefined. We induced RPE injury pharmacologically and genetically in transgenic mouse models in which microglia and systemic monocytes were separately tagged, enabling a spatial and temporal dissection of the relative contributions of microglia vs. monocytes to post-injury changes. We found that myeloid cell responses to RPE injury occur in stages: (1) an early mobilization of endogenous microglia from the inner retina to the RPE layer, followed by (2) subsequent monocyte infiltration from the retinal vasculature into the inner retina that replenishes the local myeloid cell population in a CCR2-regulated manner. These altered distributions of myeloid cells post-injury were long-lived, with recruited monocytes acquiring the distribution, markers, and morphologies of neighboring endogenous microglia in a durable manner. These findings indicate the role played by infiltrating monocytes in maintaining myeloid cell homeostasis in the retina following AMD-relevant RPE injury and provide a foundation for understanding and therapeutically modulating immune aspects in retinal disease.

PMID: 28814744 PMCID: PMC5559448


Insensitivity of PI3K/Akt/GSK3 signaling in peripheral blood mononuclear cells of age-related macular degeneration patients.

Liu X, Yao Z.
Abstract: Our recent studies with cultured retinal pigment epithelium cells suggested that overexpression of interleukin 17 receptor C (IL-17RC), a phenomenon observed in peripheral blood and chorioretinal tissues with age-related macular degeneration (AMD), was associated with altered activation of phosphatidylinositol 3-kinase (PI3K), Akt, and glycogen synthase kinase 3 (GSK3). We wondered whether or not altered PI3K, Akt, and GSK3 activities could be detected in peripheral blood mononuclear cells (PBMC) obtained from AMD patients. In the patients’ PBMC, absent or reduced serine-phosphorylation of GSK3α or GSK3β was observed, which was accompanied with increased phosphorylation of GSK3 substrates (e.g. CCAAT enhancer binding protein α, insulin receptor substrate 1, and TAU), indicative of enhanced GSK3 activation. In addition, decreased protein mass of PI3K85α and tyrosine-phosphorylation of PI3K50α was present in PBMC of the AMD patients, suggesting impaired PI3K activation. Moreover, abnormally lowered molecular weight forms of Akt and GSK3 were detected in PBMC of the AMD patients. These data demonstrate that despite the presence of high levels of IL-17RC, Wnt-3a and vascular endothelial growth factor, the PI3K/Akt/GSK3 signaling pathway is insensitive to these stimuli in PBMC of the AMD patients. Thus, measurement of PI3K/Akt/GSK3 expression and activity in PBMC may serve as a surrogate biomarker for AMD.

PMID: 28808220 PMCID: PMC5460613

Epidemiology

Eye (Lond). 2017 Aug 18. [Epub ahead of print]

Age-related macular degeneration and mortality: the Melbourne Collaborative Cohort Study.


Aims: To assess associations between features of age-related macular degeneration (AMD) and mortality.

Methods: A total of 21 129 participants from the Melbourne Collaborative Cohort Study aged 47-85 years (60% female) were assessed for AMD (2003-2007). Mortality data to December 31, 2012 were obtained through linkage with the National Death Index. Associations were assessed using Cox regression, adjusting for age, sex, smoking, region of birth, education, physical activity, diet and alcohol.

Results: Late AMD was identified in 122 (0.6%) participants, including those with choroidal neovascularisation (n=55, 0.3%), geographic atrophy (n=87, 0.4%) and reticular pseudodrusen (n=87, 0.4%). After a median follow-up period of 8.1 years, 1669 (8%) participants had died, including those from cardiovascular diseases (386), tobacco-related cancers (179), and neurodegenerative disease (157). There was evidence of an increased rate of all-cause mortality for those with choroidal neovascularisation (Hazard Ratio (HR) 1.71 95% CI 1.06-2.76) and geographic atrophy (HR 1.46 95% CI 0.99-2.16). Choroidal neovascularisation was also associated with an increased rate of cardiovascular mortality (HR 3.16 95% CI 1.62-6.15) and geographic atrophy was associated with an increased rate of death from tobacco-related cancer (HR 2.86 95% CI 1.15-7.09). Weak evidence was also present for an association between choroidal neovascularisation and death from neurodegenerative disease (HR 2.49 95% CI 0.79-7.85). Neither reticular pseudodrusen nor the earlier stages of AMD were associated with mortality.

Conclusions: Late AMD is associated with an increased rate of all-cause mortality. Choroidal neovascularisation and geographic atrophy were associated with death from cardiovascular disease and tobacco-related cancer, respectively. Eye advance online publication, 18 August 2017; doi:10.1038/eye.2017.139.

PMID: 28820184
The validity of self-report of eye diseases in participants with vision loss in the National Eye Health Survey.

Foreman J, Xie J, Keel S, van Wijngaarden P, Taylor HR, Dirani M.

Abstract: We assessed the validity and reliability of self-report of eye disease in participants with unilateral vision loss (presenting visual acuity worse than 6/12 in the worse eye and equal to or better than 6/12 in the better eye) or bilateral vision loss (presenting visual acuity worse than 6/12 in the better eye) in Australia's National Eye Health Survey. In total, 1738 Indigenous Australians and 3098 non-Indigenous Australians were sampled from 30 sites. Participants underwent a questionnaire and self-reported their eye disease histories. A clinical examination identified whether participants had cataract, age-related macular degeneration, diabetic retinopathy and glaucoma. For those identified as having unilateral or bilateral vision loss (438 Indigenous Australians and 709 non-Indigenous Australians), self-reports were compared with examination results using validity and reliability measures. Reliability was poor for all four diseases (Kappa 0.06 to 0.37). Measures of validity of self-report were variable, with generally high specificities (93.7% to 99.2%) in all diseases except for cataract (63.9 to 73.1%) and low sensitivities for all diseases (7.6% in Indigenous Australians with diabetic retinopathy to 44.1% of non-Indigenous Australians with cataract). This study suggests that self-report is an unreliable population-based research tool for identifying eye disease in those with vision loss.

PMID: 28821861 PMCID: PMC5562791

The Status of Maculopathy in Diabetes and Prediabetes Patients in a Population-Based Study Detected by Optical Coherence Tomography: The 2011 Health Examination Survey in Beijing.

Cao X, Xin Z, Li S, Qi Y, Yuan M, Zhu X, Yang JK.

OBJECTIVE: The aim of the study was to investigate the prevalence and the risk factors of maculopathy detected by optical coherence tomography (OCT) in a Chinese population with diabetes or prediabetes. Methods. 8,155 people were randomly selected to participate in the 2011 annual Health Examination Survey in Beijing. A 75 g oral glucose tolerance test (OGTT) was tested in 3760 subjects with fasting plasma glucose (FPG) ≥ 5.6 mmol/L. Of 3,760 subjects, 583 were also randomly selected to take OCT.

RESULTS: In this study population, 21 (3.95%) patients had maculopathy. Eight patients had diabetes macular edema (DME) and the prevalence was 6.72% in diabetes patients and 1.51% in all subjects. Eleven patients had age-related macular degeneration (AMD) and the prevalence was 3.36% in diabetes patients and 2.07% in all subjects. Logistic regression model confirmed that elevated HbA1c (p < 0.001) and systolic pressure (p < 0.05) made significant contributions to DME. Stepwise regression analysis revealed that HbA1c and blood creatinine were significantly independent influence factors for central subfield thickness (CST) (p = 0.01, p < 0.001).

CONCLUSIONS: High prevalence of maculopathy was found in patients with diabetes in a Chinese population. Maculopathy poses a significant public health problem in China with rapid rising trend of diabetes.

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Genetics & gene therapy


Suppression of Choroidal Neovascularization in Mice by Subretinal Delivery of Multigenic Lentiviral
Vectors Encoding Anti-Angiogenic MicroRNAs.

Askou AL, Benckendorff JNE, Holmgaard A, Storm T, Aagaard L, Bek T, Mikkelsen JG, Corydon TJ.

Abstract: Lentivirus-based vectors have been used for the development of potent gene therapies. Here, application of a multigenic lentiviral vector (LV) producing multiple anti-angiogenic microRNAs following subretinal delivery in a laser-induced choroidal neovascularization (CNV) mouse model is presented. This versatile LV, carrying back-to-back RNApolII-driven expression cassettes, enables combined expression of microRNAs targeting vascular endothelial growth factor A (Vegfa) mRNA and fluorescent reporters. In addition, by including a vitelliform macular dystrophy 2 (VMD2) promoter, expression of microRNAs is restricted to the retinal pigment epithelial (RPE) cells. Six days post injection (PI), robust and widespread fluorescent signals of eGFP are already observed in the retina by funduscropy. The eGFP expression peaks at day 21 PI and persists with stable expression for at least 9 months. In parallel, prominent AsRED co-expression, encoded from the VMD2-driven microRNA expression cassette, is evident in retinal sections and flat-mounts, revealing RPE-specific expression of microRNAs. Furthermore, LV-delivered microRNAs targeting the Vegfa gene in RPE cells reduced the size of laser-induced CNV in mice 28 days PI, as a consequence of diminished VEGF levels, suggesting that LVs delivered locally are powerful tools in the development of gene therapy-based strategies for treatment of age-related macular degeneration.

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Joint Analysis of Nuclear and Mitochondrial Variants in Age-Related Macular Degeneration Identifies Novel Loci TRPM1 and ABHD2/RLBP1.


PURPOSE: Presently, 52 independent nuclear single nucleotide polymorphisms (nSNPs) have been associated with age-related macular degeneration (AMD) but their effects do not explain all its variance. Genetic interactions between the nuclear and mitochondrial (mt) genome may unearth additional genetic loci previously unassociated with AMD risk.

METHODS: Joint effects of nSNPs and selected mtSNPs were analyzed by two degree of freedom (2df) joint tests of association in the International AMD Genomics Consortium (IAMDGC) dataset (17,832 controls and 16,144 advanced AMD cases of European ancestry). Subjects were genotyped on the Illumina HumanCoreExome array. After imputation using MINIMAC and the 1000 Genomes Project Phase I reference panel, pairwise linkage disequilibrium pruning, and quality control, 3.9 million nSNPs were analyzed for interaction with mtSNPs chosen based on association in this dataset or publications: A4917G, T5004C, G12771A, and C16069T.

RESULTS: Novel locus TRPM1 was identified with genome-wide significant joint effects (P < 5.0 × 10^-8) of two intronic TRPM1 nSNPs and AMD-associated nonsynonymous MT-ND2 mtSNP A4917G. Stratified analysis by mt allele identified an association only in 4917A (major allele) carriers (P = 4.4 × 10^-9, odds ratio [OR] = 0.90, 95% confidence interval [CI] = 0.87-0.93). Intronic and intergenic ABHD2/RLBP1 nSNPs demonstrated genome-wide significant joint effects (2df joint test P values from 1.8 × 10^-8 to 4.9 × 10^-8) and nominally statistically significant interaction effects with MT-ND5 synonymous mtSNP G12771A. Although a positive association was detected in both strata, the association was stronger in 12771A subjects (P = 0.0020, OR = 2.17, 95% CI = 1.34-3.60).

CONCLUSIONS: These results show that joint tests of main effects and gene-gene interaction reveal associations at some novel loci that were missed when considering main effects alone.

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On variants and disease-causing mutations: Case studies of a SEMA4A variant identified in inherited blindness.

Bryant L, Lozynska O, Han G, Morgan JIW, Gai X, Maguire AM, Aleman T, Bennett J.

Abstract: The p.R713Q variant of the semaphorin-4a-encoding gene, SEMA4a, has been reported to cause autosomal dominant retinitis pigmentosa. Here we show three families with retinal degeneration in which unaffected family members are either homozygous or heterozygous for the variant. The p.R713Q variant in SEMA4A is insufficient to cause either autosomal recessive or autosomal dominant retinitis pigmentosa and is unlikely to be pathogenic.

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Diet, lifestyle & low vision


Effects of Lycium barbarum on the Visual System.

Manthey AL, Chiu K, So KF.

Abstract: Lycium barbarum (wolfberry, gogi berry, gouqizi, ) is one of the most widely used Chinese herbal medicines (CHMs) and is also one of the most scientifically studied. Indeed, the polysaccharide component of this berry (LBP) has been shown to have antioxidant, antiinflammatory, antiexcitotoxic, and antiapoptotic properties. These properties make it a particularly useful treatment option for the ocular environment. Although there are a handful of studies investigating the use of LBP to treat diseases affecting the lens, the vast majority of the published literature investigating LBP in the visual system focus on the retina. In this chapter, we have described what is currently understood concerning the effects of LBP treatment on various retinal diseases, including glaucoma, ischemia/reperfusion, age-related macular degeneration, retinitis pigmentosa, and diabetic retinopathy. We then describe the functions attributed to LBP using other cellular contexts to elucidate the full mechanisms this CHM utilizes in the retina. By making connections between what is known about the function of LBP in a variety of tissues and its function as a therapy for retinal degenerative diseases, we hope to further emphasize the continued use of this CHM in clinical medicine in addition to providing a platform for additional study.

PMID: 28807155


Plasticity beyond V1 - Reinforcement of motion perception upon binocular central retinal lesions in adulthood.

Burnat K, Hu TT, Kossut M, Eysel UT, Arckens L.

Abstract: Induction of a central retinal lesion in both eyes of adult mammals is a model for macular degeneration and leads to retinotopic map reorganization in the primary visual cortex (V1). Here we characterized the spatio-temporal dynamics of molecular activity levels in the central and peripheral representation of five higher order visual areas, V2/18, V3/19, V4/21a, V5/PMLS, area 7, and V1/17, in adult cats with central 10° retinal lesions (both sexes), by means of real-time PCR for the neuronal activity reporter gene zif268. The lesions elicited a similar, permanent reduction in activity in the center of the lesion projection zone of area V1/17, V2/18, V3/19 and V4/21a, but not in the motion-driven V5/PMLS, which instead displayed an increase in molecular activity at 3 months postlesion, independent of visual field coordinates. Also area 7 only displayed decreased activity in its LPZ in the first weeks post-lesion and...
increased activities in its periphery from 1 month onwards. Therefore we examined the impact of central vision loss on motion perception using random dot kinematograms to test the capacity for Form from Motion detection based on direction and velocity cues. We revealed that the central retinal lesions either do not impair motion detection or even result in better performance, specifically when motion discrimination was based on velocity discrimination. In conclusion, we propose that foveal retinal damage leads to enhanced peripheral vision by sensitizing the visual system for motion processing relying on feedback from V5/PMLS and area 7. SIGNIFICANCE STATEMENT Central retinal lesions, a model for macular degeneration, result in functional reorganization of the primary visual cortex. Examining the level of cortical reactivation with the molecular activity marker zif268 revealed reorganization in visual areas outside V1. Retinotopic lesion projection zones typically display an initial depression in zif268 expression, followed by partial recovery with post-lesion time. Only the motion-sensitive area V5/PMLS shows no decrease, and even a significant activity increase at 3 months post retinal lesion. Behavioral tests of motion perception found no impairment and even better sensitivity to higher random dot stimulus velocities. We demonstrate that the loss of central vision induces functional mobilization of motion-sensitive visual cortex, resulting in enhanced perception of moving stimuli.

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